

ATGAGCTATTACGGAAGTAGCTACCGGATTGTCAATGTGGACTCCAAATATCCAGGCTATCCTCC
AGAGCATGCCATCGCTGAGAAGAGAAGAGCAAGAAGGCGCTTGCTCCACAAAGATGGCAGCTGTA
ATGTGTACTTTAAACACATTTTTGGAGAATGGGGGAGCTACATGGTTGATATTTTTTACCACTCTT
GTGGATACCAAGTGGCGCCATATGTTTATAATATTTTCTCTGTCTTACATTCTCTCCTGGTTGAT
ATTTGGTTCCATATTTTGGCTCATAGCCTTTCATCACGGAGACCTATTAAGCGATCCAGATATCA
CCCCTTGTTGTTGACAACGTGCATTTCATTTACGGCTGCATTTTTTATTCTCCCTGGAGACCCAGACC
ACCATTTGGATACGGTTACCGCTGTGTCACCGAAGAGTGCTCTGTGGCTGTACTGACAGTGATCCT
TCAGTCCATCCTCAGCTGCATCATAAACACCTTCATCATTTGGAGCAGCCTTGGCAAAGATGGCAA
CTGCCCCGGAAGAGAGAGCCAGACCATAACGCTTCAGCTATTTTGCCCTCATTTGGTATGAGAGACGGG
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AGCCCAACTTCTGCGCTATTTCAGAAGACAGTGAAGGGAGGATGACGATGGCGTTTAAAGACCTCA
AACTCGTCAATGACCAGATAATCCTGGTAACTCCAGTGACTATTGTCCATGAAATTGACCATGAG
AGCCCTCTGTATGCCCTTGACCGCAAGGCAGTGGCCAAAGATAATTTTCGAGATTCTGGTGACATT
TATTTATACTGGTGATTCCACTGGGACATCCCACCAGTCCAGAAGTTCCTACATCCCCAGAGAAA
TTCTCTGGGGCCACAGGTTTCATGATGTATTGGAAGTGAAGAGAAAGTACTACAAGGTGAACTGC
TTGCAGTTTGAAGGAAGCGTGGAAGTCTACGCCCCCTTTTGCAGTGCCAAACAACTGGACTGGAA
GGACCAACAACCTCAACAACCTTGAGAGAAAACGTCCCCTGCCCCGAGGATCCTGCAATTCTGACACCA
ACACCAGGAGGCGGTCCTTCAGCGCAGTTGCCGTGGTGAGCAGCTGTGAGAACCCAGAGGAGACC
GTCCTGTCCCCACAAGATGAATGTAAGGAGATGCCCTATCAGAAAGCCCTCCTGACTTTAAATAG
GATCTCCATGGAATCCCAGATG (SEQ ID NO:1)

FIGURE 1

MSYYGSSYRIVNVDSKYPGYPPEHAIAEKRRARRRLLHKDGS CNVYFKHIFGEWGSYMVDIFTT
LVDTKWRHMFIIIFSLSYILSWLIFGSIFWLI AFHHGDLLSDPDITPCVDNVHSFTA AFLFSLET
QTTIGYGYRCVTEEC SVAVLTVILQSILSCIINTFIIGAALAKMATARKRAQTIRFSYFALIGM
RDGKPCLMWRIGDFRPNHVVEGTVRAQLLRYS EDEGRMTMAFKDLKLVNDQIILVTPVTIVHE
IDHESPLYALDRKAVAKDNFEILVTFIYTG DSTGTSHQSRSSYIPREILWGHRFHDVLEV KRKY
YKVNCLQFEGSVEVYAPFCSAKQLDWKDQQLNNLEKTS PARGSCNSDTNTRRRSFS AVAVVSSC
ENPEETVLS PQDECKEMPYQKALLTLNRISMESQM (SEQ ID NO:2)

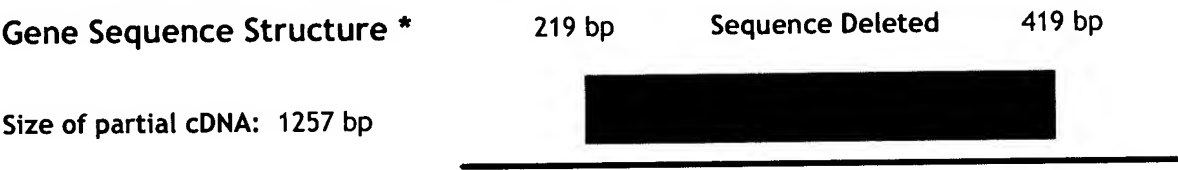
FIGURE 2

underlined = deleted in targeting construct

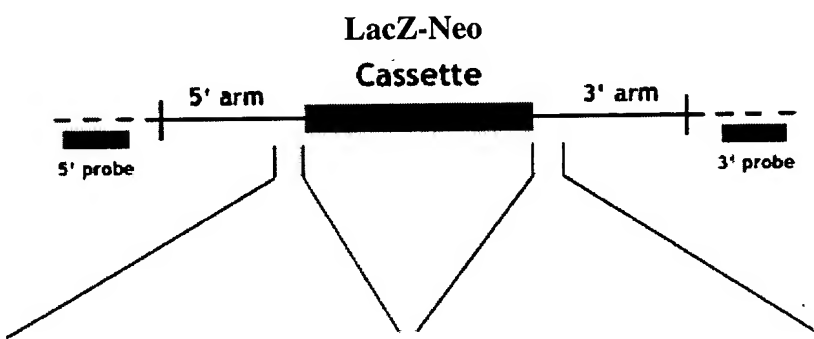
BOLD = sequence flanking Neo insert in targeting construct

ATGAGCTATTACGGAAGTAGCTACCGGATTGTCAATGTGGACTCCAAATATCCAGGCTAT
 CCTCCAGAGCATGCCATCGCTGAGAAGAGAAGAGCAAGAAGGCGCTTGCTCCACAAAGAT
 GGCAGCTGTAATGTGTACTTTAAACACATTTTGGAGAATGGGGGAGCTACATGGTTGAT
 ATTTTACCACCTCTGTGGATACCAAGTGGCGCCATATGTTTCATAATATTTTCTCTGTCT
 TACATTCTCTCCTGGTTGATATTTGGTTCCATATTTGGCTCATAGCCTTTCATCACGGA
 GACCTATTAAGCGATCCAGATATCACCCCTTGTGTTGACAACGTGCATTTCATTTACGGCT
 GCATTTTATTCTCCCTGGAGACCCAGACCACCATTTGGATACGGTTACCGCTGTGTCACC
 GAAGAGTGCTCTGTGGCTGTACTGACAGTGATCCTTCAGTCCATCCTCAGCTGCATCATA
 AACACCTTCATCATTTGGAGCAGCCTTGGCAAAGATGGCAACTGCCCGGAAGAGAGCCCAG
 ACCATACGCTTCAGCTATTTTGGCCCTCATTGGTATGAGAGACGGGAAGCCTTGCCCTCATG
 TGGCGCATAGGTGACTTCCGACCAAACCATGTGGTAGAGGGGCACGGTGAGAGCCCAACTT
 CTGCGCTATTCAGAAGACAGTGAAGGGAGGATGACGATGGCGTTTAAAGACCTCAAACCTC
 GTCAATGACCAGATAATCCTGGTAACTCCAGTGACTATTGTCCATGAAATTGACCATGAG
 AGCCCTCTGTATGCCCTTGACCGCAAGGCAGTGGCCAAAGATAATTTTCGAGATTCTGGTG
 ACATTTATTTATACTGGTGATTCCACTGGGACATCCCACCAGTCCAGAAGTTCTTACATC
 CCCAGAGAAATTCCTGTTGGGGCCACAGGTTTCATGATGTATTGGAAGTGAAGAGAAAGTAC
 TACAAGGTGAACTGCTTGCAGTTTGAAGGAAGCGTGAAGTCTACGCCCCCTTTTGCAGT
 GCCAAACAACCTGGACTGGAAGGACCAACAACCTCAACAACCTTGGAGAAAACGTCCCTGCC
 CGAGGATCCTGCAATTCTGACACCAACACCAGGAGGCGGTCTTCAGCGCAGTTGCCGTG
 GTGAGCAGCTGTGAGAACCCAGAGGAGACCGTCTCTGTCCTCCACAAAGATGAATGTAAGGAG
 ATGCCCTATCAGAAAGCCCTCCTGACTTTAAATAGGATCTCCATGGAATCCCAGATG

FIGURE 3



Targeting Vector*
(genomic sequence)



Arm Length:
5': 1.5 kb
3': 3.5 kb

———— Targeting Vector
----- Endogenous Locus

* Not drawn to scale

<p>5' >AGCTACAGGATCGTCAATGTG GACTCCAAATATCCAGGCTATCCT CCAGAGCATGCCATCGCTGAGAAG AGAAGAGCAAGAAGGCGCTTGCTC CACAAAGATGGCAGCTGTAATGTG TACTTTAAACACATTTTGGAGAA TGGGGGAGCTACATGGTTGATATT TTTACCACTCTTGTGGATACCAAG TGGCGCCATAT<3' (SEQ ID NO:3)</p>	<p>5' >CGAAGAGTGCTCTGTGGCTGT ACTGACAGTGATCCTTCAGTCCAT CCTCAGCTGCATCATAAACACCTT CATCATTGGAGCAGCCTTGGCAAA GATGGCAACTGCCCGGAAGAGAGC CCAGACCATACGCTTCAGCTATTT TGCCCTCATTGGTATGAGAGACGG GAAGCTTTGCCTCATGTGGCGCAT AGGTGACTTCC<3' (SEQ ID NO:4)</p>
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FIGURE 4

Genotype	Age (Days)	Average Highest Voltage (volts)	No Stimulation	P080	P085	P090	P100	P110	P120	PP080P120	PP085P120	PP090P120	PP100P120	PP090P110
-/-	76	30.8	20.6	0.0	0.0	343.7	1198.3	1821.2	2315.9	1927.8	0.0	544.4	218.6	0.0
-/-	77	16.8	19.8	0.0	0.0	42.4	403.3	1154.4	1883.7	1476.6	0.0	1282.2	702.1	0.0
-/-	77	19.7	22.6	0.0	0.0	55.0	458.9	1751.5	2493.1	2036.3	0.0	716.4	207.1	0.0
-/-	78	35.8	50.3	0.0	0.0	79.1	381.4	1495.0	2250.3	1534.7	0.0	463.8	181.6	0.0
-/-	77	30.3	45.4	0.0	0.0	54.1	140.6	446.7	969.3	813.4	0.0	482.4	188.5	0.0
-/-	77	20.6	23.8	0.0	0.0	98.1	450.7	1840.5	2369.6	2639.2	0.0	1268.4	348.3	0.0
-/-	77	37.5	27.8	0.0	0.0	97.6	439.5	1367.7	1674.3	1670.8	0.0	437.6	122.0	0.0
-/-	73	42.4	34.2	0.0	0.0	112.3	378.5	1088.9	1800.2	1794.9	0.0	902.8	175.8	0.0
-/-	73	23.7	35.2	0.0	0.0	163.1	671.4	1753.9	1807.1	1256.9	0.0	823.3	272.6	0.0
+/+	78	51.1	62.5	0.0	0.0	38.9	115.2	976.7	1469.2	1429.2	0.0	701.6	168.0	0.0
+/+	76	16.4	19.7	0.0	0.0	25.1	486.3	1173.8	1577.7	1745.7	0.0	929.2	282.7	0.0
+/+	77	23.2	21.3	0.0	0.0	24.1	284.6	2023.0	2686.0	2379.4	0.0	1543.1	832.1	0.0
+/+	78	21.7	27.0	0.0	0.0	70.2	334.5	618.6	641.1	473.4	0.0	180.7	97.3	0.0
+/+	77	31.2	40.5	0.0	0.0	37.0	106.0	229.5	308.5	393.1	0.0	114.2	76.2	0.0
+/+	77	25.6	16.5	0.0	0.0	19.7	45.8	348.6	466.8	350.7	0.0	104.5	42.9	0.0
+/+	77	24.6	23.7	0.0	0.0	31.7	497.5	1420.5	1992.7	1677.8	0.0	1194.8	279.7	0.0
+/+	77	48.7	49.8	0.0	0.0	34.6	78.6	538.5	1738.3	1712.9	0.0	930.1	325.2	0.0
+/+	73	70.8	142.9	0.0	0.0	60.6	118.2	370.6	291.0	295.4	0.0	151.0	66.8	0.0
+/+	73	42.4	28.2	0.0	0.0	38.0	70.7	614.4	1312.0	861.8	0.0	791.3	180.7	0.0

FIGURE 5